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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,568	07/11/2003	Kai W. Wucherpfennig	DFS-04401	3949
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FOLEY HOAG, LLP PATENT GROUP, WORLD TRADE CENTER WEST 155 SEAPORT BLVD BOSTON, MA 02110			DIBRINO, MARIANNE NMN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/617,568	Applicant(s) WUCHERPENNIG ET AL.
	Examiner DiBrino Marianne	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on **3/26/08 & 12/29/08**.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) **1,3 and 13-50** is/are pending in the application.

4a) Of the above claim(s) **19-50** is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) **1,3,13-18** is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/12/09

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date _____

5) Notice of Informal Patent Application

6) Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/29/08 has been entered.

Applicant's amendments filed 3/26/08 and 12/29/08 are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I and species of SEQ ID NO: 36 as the spaceholder molecule and effector component that is biotin in Applicant's responses filed 8/9/06 and 11/27/06.

Claims 1, 3 and 13-18 read on the elected species and are presently being examined.

The search has been extended to include SEQ ID NO: 1 recited in instant base claim 1.

3. Applicant's amendment filed 12/29/08 has overcome the prior rejection of record of claims 1, 3, 7-10 and 13-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al* (Nature. 1994, 369: 151-154, of record) and Natarajan *et al* (J. Immunol. 1999, 162: 4030-4036).

Zhong *et al* teach an MHC class II compound comprising the MHC class II α chain and the MHC class II β chain, the β chain linked to the mouse Ii 89-100 invariant chain CLIP peptide via a linker, and the compound further associated with a chemical dye on SDS-PAGE or associated with a radiolabel upon metabolic labeling, *i.e.*, associated with an

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effector component (see entire reference, especially materials and methods, Figure 1 and Results section).

Zhong *et al* do not teach wherein the linker is a processable linker.

Kozono *et al* teach an MHC class II compound comprising the extracellular domains of the α and β chains of MHC class II, and a peptide attached by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site, wherein the peptide is a 13-mer peptide that binds to the binding groove formed by the MHC class II chains, said compound being immobilized by an anti- β chain monoclonal antibody or absorbed to tissue culture plate wells, *i.e.*, the MHC class II component is linked to the effector component. Kozono *et al* teach that it is possible to produce a covalent complex of peptide and class II protein which can be recognized by most T cells specific for the combination, and that structures of this type would be useful in experiments on the structure of TCR ligand interactions. Kozono *et al* teach that in the case of the IA molecule, it may be the only way to generate soluble class II/peptide complexes in reasonable quantities (see entire reference, especially abstract, paragraph spanning columns 1-2 on page 151, Figure 1A, Figure 2 and 4 legends, paragraph spanning columns 1-2 on page 154).

Natarajan *et al* teach incubating insect cell produced class II molecules with low affinity peptide(s) (see entire article). Natarajan *et al* further teach "One of the problems that has plagued MHC/class II peptide binding analyses is the heterogeneity of the MHC molecules. Recombinant MHC produced in insect cells aggregate in different forms while the molecules purified from cellular sources are mostly occupied by endogenous peptides. consequently, MHC molecules in various conformations complicate kinetic analysis. Furthermore, we...and others...have shown that the empty molecules lose their peptide binding activity over a period of time. The use of class II heterodimers that are dissociating from their peptide ligand overcomes this problem and provides a homogeneous pool of MHC molecules for determination of peptide binding (especially fourth full paragraph at column 1 on page 4035).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the construct taught by Zhong *et al*, but with a processable linker such as taught by Kozono *et al* for their class II MHC/peptide molecule and including a detectable label.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a class II/MHC peptide molecule such as taught by Zhong *et al*, but containing a low or intermediate affinity binding peptide with free termini such as taught by Kozono *et al*, especially in light of the teaching of Natarajan *et al* that it is desirable to provide a homogeneous pool of insect-cell-produced molecules in the process of dissociating from their peptide ligand each having the same conformation for use in determination of peptide binding, and further in light of the

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teaching of Kozono *et al* that covalent complex of peptide and class II protein would be useful in experiments on the structure of TCR ligand interactions.

Claims 16-18 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

With regard to the limitation "PVS₁KM₂RM₃ATP₄LLMQA (SEQ ID NO: 1)" recited in instant base claim 1, SEQ ID NO: 1 is comprised in the Ii 89-100 invariant chain CLIP peptide taught by the primary reference, and the said base claim recites "an isolated MHC class II compound comprising...a spaceholder molecule, wherein the spaceholder molecule is selected from the group consisting of PVS₁KM₂RM₃ATP₄LLMQA (SEQ ID NO: 1)....". Hence the said claim encompasses a space holder molecule that is SEQ ID NO: 1 with additional N-and/or C-terminal flanking sequences.

Therefore the claimed MHC class II compound appears to be similar to the MHC class II compound of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the MHC class II compound of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on page 9, briefly that claim 1 has been amended to recite SEQ ID NO: 1-5 and 36, and none of the references either alone or in combination teach or suggest each and every element of the instant claims because the references fail to disclose the spaceholder molecules of the amended claims.

However, given the open transitional language recited in instant claim 1, the references do teach the claimed invention as enunciated *supra* in the instant rejection.

6. Claims 1, 3, 14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al* (Nature. 1994, 369: 151-154, of record), Natarajan *et al* (J. Immunol. 1999, 162: 4030-4036), Malcherek *et al* (J. Exp. Med. 1995, 181: 527-536, IDS reference) and DiBrino *et al* (J. Biol. Chem. 1994, 269(51): 32426-32434, of record).

Zhong *et al* teach an MHC class II compound comprising the MHC class II α chain and the MHC class II β chain, the β chain linked to the mouse Ii 89-100 invariant chain CLIP peptide via a linker, and the compound further associated with a chemical dye on SDS-PAGE or associated with a radiolabel upon metabolic labeling, *i.e.*, associated with an effector component (see entire reference, especially materials and methods, Figure 1 and Results section).

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Zhong *et al* do not teach wherein the MHC class II compound comprises a placeholder molecule that is AAMAAAAAAAMA (SEQ ID NO: 2), AAFAAAAAAAA (SEQ ID NO: 4), or AAMAAAAAAA (SEQ ID NO: 3), nor wherein the linker is a cleavable linker.

Kozono *et al* teach an MHC class II compound comprising the extracellular domains of the α and β chains of MHC class II, and a peptide attached by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site, wherein the peptide is a 13-mer peptide that binds to the binding groove formed by the MHC class II chains, said compound being immobilized by an anti- β chain monoclonal antibody or absorbed to tissue culture plate wells, *i.e.*, the MHC class II component is linked to the effector component. Kozono *et al* teach that it is possible to produce a covalent complex of peptide and class II protein which can be recognized by most T cells specific for the combination, and that structures of this type would be useful in experiments on the structure of TCR ligand interactions. Kozono *et al* teach that in the case of the IA molecule, it may be the only way to generate soluble class II/peptide complexes in reasonable quantities (see entire reference, especially abstract, paragraph spanning columns 1-2 on page 151, Figure 1A, Figure 2 and 4 legends, paragraph spanning columns 1-2 on page 154).

Natarajan *et al* teach incubating insect cell produced class II molecules with low affinity peptide(s) (see entire article). Natarajan *et al* further teach "One of the problems that has plagued MHC/class II peptide binding analyses is the heterogeneity of the MHC molecules. Recombinant MHC produced in insect cells aggregate in different forms, while the molecules purified from cellular sources are mostly occupied by endogenous peptides. Consequently, MHC molecules in various conformations complicate kinetic analysis. Furthermore, we...and others...have shown that the empty molecules lose their peptide binding activity over a period of time. The use of class II heterodimers that are dissociating from their peptide ligand overcomes this problem and provides a homogeneous pool of MHC molecules for determination of peptide binding (especially fourth full paragraph at column 1 on page 4035).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the construct taught by Zhong *et al*, but with a processable linker such as taught by Kozono *et al* for their class II MHC/peptide molecule and including a detectable label.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a class II/MHC peptide molecule such as taught by Zhong *et al*, but containing a low or intermediate affinity binding peptide with free termini such as taught by Kozono *et al*, especially in light of the teaching of Natarajan *et al* that it is desirable to provide a homogeneous pool of insect-cell-produced molecules in the process of dissociating from their peptide ligand each having the same conformation for use in determination of peptide binding, and further in light of the

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teaching of Kozono *et al* that covalent complex of peptide and class II protein would be useful in experiments on the structure of TCR ligand interactions.

Malcherek *et al* teach that the human CLIP peptide amino acid residues 105-117 (SKM^{MR}ATPLLMQ^A) conferred about the same binding as the CLIP 97-120 peptide (LPKPPPKP^VSKM^RATPLLMQ^ALPM, Figure 2 and the paragraph spanning pages 530-531). Malcherek *et al* further teach that Met107 is the main anchor residues for CLIP to bind different HLA class II alleles and isotypes such as HLA-DR17, -DR1 and -DR4Dw4 (first full paragraph at column 2 on page 532). Malcherek *et al* teach that with regard to CLIP binding to HLA-DR17, Met 107 and Met115 were important, as an Ala scan (*i.e.*, replacing one amino acid in the peptide sequence with Ala, and making a series of peptides, each having only one substitution) of CLIP 106-117 showed that substitution with Ala at these positions led to a decrease of the binding capacity of at least 100- and 10-20 fold, respectively, whereas Phe or Leu substitution for Met115 led to a lesser decrease of the binding capacity and Phe or Leu substitution for Met 107 maintained the parental binding capacity of CLIP or even improved it. Aspartate substitution of these residues completely disrupted binding (paragraph spanning pages 538-529).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the amino terminus of the CLIP 105-117 peptide out sequentially (as well as the carboxy terminus), including making a peptide with the sequence PVSKM^RATPLLMQ^A (amino acid residues 103-117), in order to determine if binding fully commensurate with the CLIP 97-120 peptide could be obtained, and to have made a construct of the structure taught by the combined references, but using a human HLA class II molecule such as HLA-DR17 taught by Malcherek *et al* that binds the CLIP 105-117 and the CLIP 97-120 peptide, and the extended peptides such as CLIP 103-117.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study a human HLA and CLIP taught by Malcherek *et al* in the context of the molecule of the structure taught by the combined references.

DiBrino *et al* teach making poly-Ala peptides having residues deemed important for binding to an MHC molecule as well as performing an Ala scan on a peptide to study the contribution of each said residue for binding (especially Table III and column 2 on page 32429).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a peptide with the sequence AAMAAAAAAAMA^A, AAFAAAAAAA, or AAMAAAAAA, *i.e.*, one having the two residues deemed important by Malcherek *et al*, or one having the Met 107 deemed important for binding to HLA-DR4w4, or one with a Phe substituent for Met 107 that improves binding of the parental peptide as taught by Malcherek *et al*, and to have made a construct such as taught by the combined references.

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study binding of human HLA class II because Malcherek *et al* only used Ala scan peptides to assess the contribution of certain residues, said Ala scan peptides have the native amino acid residues at every position except for the scan position where Ala is substituted, and DiBrino *et al* teach that making Ala scan peptides as well as poly-Ala peptides is useful for studying the contribution of each residue for binding to an MHC molecule.

Claims 16-18 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

With regard to the limitation "PVS₁KM₂RM₃ATP₄L₅L₆M₇Q₈A (SEQ ID NO: 1)" recited in instant base claim 1, SEQ ID NO: 1 is comprised in the Ii 89-100 invariant chain CLIP peptide taught by the primary reference, and the said base claim recites "an isolated MHC class II compound comprising...a spaceholder molecule, wherein the spaceholder molecule is selected from the group consisting of PVS₁KM₂RM₃ATP₄L₅L₆M₇Q₈A (SEQ ID NO: 1)..." . Hence the said claim encompasses a space holder molecule that is SEQ ID NO: 1 with additional N-and/or C-terminal flanking sequences. Also, Malcherek *et al* teach a peptide comprising the CLIP peptide that comprises SEQ ID NO: 1.

Therefore the claimed MHC class II compound appears to be similar to the MHC class II compound of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the MHC class II compound of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on page 10, briefly that claim 1 has been amended to recite SEQ ID NO: 1-5 and 36, none of the references either alone or in combination teach or suggest each and every element of the instant claims because the references fail to disclose the spaceholder molecules of the amended claims, and one skilled in the art at the time of invention would have had no motivation to modify the sequences that are disclosed in Malcherek *et al* and DiBrino *et al* so as to generate the spaceholder sequences of the amended claims.

However, given the open transitional language recited in instant claim 1, the references do teach the claimed invention and motivation exists to combine the references as enunciated *supra* in the instant rejection.

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7. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al* (Nature. 1994, 369: 151-154, of record) and Natarajan *et al* (J. Immunol. 1999, 162: 4030-4036) as applied to claims 1, 3, 14 and 16-18 above, and further in view of Crawford *et al* (Immunity. 1998, 8: 675-682, IDS reference).

The combination of Zhong *et al*, Kozono *et al* and Natarajan *et al* have been discussed supra, hereafter referred to as "the combined references."

The combined references do not teach wherein the effector component is biotin.

Crawford *et al* teach multimerization of MHC class II/peptide complexes by including a peptide tag that could be biotinylated, biotinylating the MHC complexes, mixing the MHC class II/peptide complexes with PE/SA (especially materials and methods). Crawford *et al* teach that multimeric soluble MHC class II molecules stably occupied with covalently attached peptides bind with appropriate specificity to T cells, and with higher affinity than the monomeric MHC class II complexes (abstract). Crawford *et al* also teach genetically coupling the peptide of interest to the N terminus of the β chain of class II MHC via a flexible linker so that the peptide is covalently attached to the MHC molecule and stable occupies the peptide binding groove during biosynthesis (last paragraph at column 1 on page 679). Crawford *et al* teach that when MHC/peptide monomers are multimerized, they achieve much higher avidities for the $\alpha\beta$ TCR on the T cell surface (first paragraph at column 2 on page 675).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have multimerized the complexes taught by the combined references, plus or minus the leucine zipper peptides, using the methodology of Crawford *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the avidity of reactivity of the complexes with T cells as taught by Crawford *et al*.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on pages 10-11, briefly that claim 1 has been amended to recite SEQ ID NO: 1-5 and 36, and none of the references either alone or in combination teach or suggest each and every element of the instant claims because the references fail to disclose the spaceholder molecules of the amended claims.

However, given the open transitional language recited in instant claim 1, the references do teach the claimed invention as enunciated supra in the instant rejection.

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8. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong *et al* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al* (Nature. 1994, 369: 151-154, of record), Natarajan *et al* (J. Immunol. 1999, 162: 4030-4036), Malcherek *et al* (J. Exp. Med. 1995, 181: 527-536, IDS reference) and DiBrino *et al* (J. Biol. Chem. 1994, 269(51): 32426-32434, of record) as applied to claims 1,3, 14 and 16-18 above, and further in view of Crawford *et al* (Immunity. 1998, 8: 675-682, IDS reference).

The combination of Zhong *et al*, Kozono *et al*, Natarajan *et al*, Malcherek *et al* and DiBrino *et al* have been discussed *supra*, hereafter referred to as "the combined references."

The combined references do not teach wherein the effector component is biotin.

Crawford *et al* teach multimerization of MHC class II/peptide complexes by including a peptide tag that could be biotinylated, biotinylating the MHC complexes, mixing the MHC class II/peptide complexes with PE/SA (especially materials and methods). Crawford *et al* teach that multimeric soluble MHC class II molecules stably occupied with covalently attached peptides bind with appropriate specificity to T cells, and with higher affinity than the monomeric MHC class II complexes (abstract). Crawford *et al* also teach genetically coupling the peptide of interest to the N terminus of the β chain of class II MHC via a flexible linker so that the peptide is covalently attached to the MHC molecule and stable occupies the peptide binding groove during biosynthesis (last paragraph at column 1 on page 679). Crawford *et al* teach that when MHC/peptide monomers are multimerized, they achieve much higher avidities for the $\alpha\beta$ TCR on the T cell surface (first paragraph at column 2 on page 675).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have multimerized the complexes taught by the combined references, plus or minus the leucine zipper peptides, using the methodology of Crawford *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the avidity of reactivity of the complexes with T cells as taught by Crawford *et al*.

Applicant has not argued this rejection, however the Examiner's response to Applicant's arguments to the combined references, *i.e.*, that claim 1 has been amended to recite SEQ ID NO: 1-5 and 36, and none of the references either alone or in combination teach or suggest each and every element of the instant claims because the references fail to disclose the spaceholder molecules of the amended claims, enunciated *supra*, applies herein.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
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Group 1640
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March 10, 2009

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644